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DANIEL R MCCLURE
THOMAS KAYDEN HORSTEMEYER & RISLEY
100 GALLERIA PARKWAY SUITE 1500
ATLANTA, GA 30339-5948

EXAMINER	
KUBELIK, ANNE R	
ART UNIT	PAPER NUMBER
1638	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/445,480	Applicant(s) JONGSMA ET AL.	
	Examiner Anne Kubelik	Art Unit 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-23 is/are pending in the application.

4a) Of the above claim(s) 1-7,19-23 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 8-18 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group II (claims 8-18) in Paper No. 17 is acknowledged. The traversal is on the ground(s) that no restriction requirement was made in the International phase of this application, that a search on all the claims will require a search in the same class and subclass, and that filing four separate applications would be an unreasonable burden on the Applicant. This is not found persuasive because US examiners are not bound by the choice of an examiner in the European Patent Office not to do a Lack of Unity requirement. The methods of the different groups have different staring materials, different method steps, and different end products; thus, they require different and nonoverlapping searches. Searching and examining four different inventions would be an undue burden on the Office.

Claims 1-7 and 19-23 are withdrawn from consideration, as being drawn to nonelected inventions. Claims 8-18 are examined.

The requirement is still deemed proper and is therefore made FINAL.

2. The drawings are objected to for the reasons indicated on accompanying form PTO 948. Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

3. Reference German Patent No. 0348348 in the information disclosure statement filed 13 November, 2000, fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of this non-English language patent. The reference has been placed in the

application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

The SEQ ID NO: must accompany all sequences and all references to sequences within the specification and claims (see, for example, pg 43, lines 5, 12 and 14 and claim 15).

Full compliance with the sequence rules is required in response to this Office action. A complete response to this Office action must include both compliance with the sequence rules and a response to the issues set forth below. Failure to fully comply with both of these requirements in the time period set forth in this Office action will be held to be non-responsive.

5. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract, directed to the elected invention, on a separate sheet is required.

Claim Objections

6. Claim 8 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only and cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). For purposes of examination,

claim 8 has been treated as though it were solely dependent upon claim 1. Such treatment does not relieve Applicant of the responsibility of responding to this objection.

7. Claim 8 is objected to for being dependent upon a non-elected claim.

8. Claims 15 and 17 are objected to because of the following informalities:

Claim 15 recites an improper article before "amino acid" in line 2.

Claim 17 recites an improper article before "biologically" in line 1.

9. Claim 15 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The nucleic acids encoding "functional derivatives" of SEQ ID NO:2 claimed in claim 15 are broader than the nucleic acids claimed in parent claim 14.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 8-15 and 17-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a multitude of DNA molecules that encode proteins with type I repeated thyroglobulin domains where the proteins control insects, plants transformed with

those DNA molecules, and methods of using them. In contrast, the specification only describes a coding sequence from sea anemone that comprises SEQ ID NO:1.

The specification fails to describe the structural features of all the DNA molecules that encode cysteine protease inhibitors with type I repeated thyroglobulin domains and fails to describe the structural features that distinguish proteins with type I repeated thyroglobulin domains that are cysteine protease inhibitors from other proteins with type I repeated thyroglobulin domains.

Hence, Applicant has not, in fact, described DNA molecules that encode cysteine protease inhibitors with type I repeated thyroglobulin domains where the proteins control insects within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016 at page 1021:

> A gene is a chemical compound, albeit a complex one, and ... conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials .... Conception does not occur unless one has a mental picture of the structure of the chemical or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by it principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.

See *In re Shokal,* 113 USPQ 283, (CCPA 1957) at pg 285

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189 ; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus

> comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary. ...
> We are of the opinion that a genus containing such a large number of species cannot properly be identified by the mere recitation or reduction to practice of four or five of them. As was pointed out by the examiner, four species might be held to support a genus, if such genus is disclosed in clear language; but where those species must be relied on not only to illustrate the genus but to define what it is, the situation is otherwise.

12. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is directed to specific plasmid, pCAB1. Since the plasmid is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the plasmid is not so obtainable or available, a deposit of a microorganism containing said plasmid may satisfy the requirements of 35 USC 112. The specification does not disclose a repeatable process to obtain the plasmid, and it is not apparent if the plasmid is readily available to the public. Thus, a deposit is required for enablement purposes.

If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the enforceable life of the patent, whichever is longer;
(d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and,

(e) the deposit will be replaced if it should ever become inviable.

13. Claims 8-15 and 17-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of protecting a plant against insect or nematode infestation by transformation with a nucleic acid encoding equistatin, does not reasonably provide enablement for a method of protecting a plant against insect or nematode infestation by transformation with any nucleic acid encoding a cysteine protease inhibitor comprising a type I thyroglobulin domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to a method of protecting a plant against insect or nematode infestation by transformation with any of a multitude of nucleic acids encoding a cysteine protease inhibitor comprising a type I thyroglobulin domain or a "functional derivative" of SEQ ID NO:2, plants and cells transformed with such nucleic acids, and expression vectors for that transformation.

The instant specification, however, only provides guidance for the isolation of domains 2-3 of the equistatin protein and kinetic analysis of the ability of this fragment to inhibit cathepsin D (example 1), cloning of the cDNA for equistatin (SEQ ID NO:1; example 2), expression of the cDNA in *Escherichia coli* (example 3), purification of the equistatin protein from the *E. coli* cells (examples 3-4), *in vitro* inhibition of Colorado potato beetle midgut protease and comparison with the activity of other cysteine protease inhibitors (example 5), *in vitro* inhibition of proteases from adult western flower thrips, leafminer flies, and western corn rootworms (example 6), toxicity assays of equistatin towards Colorado potato beetle larvae (example 7), *in vivo* assay of the effect

of equistatin on oviposition rate of thrips (example 8), modification of the cDNA for expression in plants (example 9), construction of plant vectors comprising the equsitation coding region (example 10), transformation of potato with those plant vectors (example 11), and assay of Colorado potato beetle larvae on those transgenic plants (example 12).

The instant specification fails to provide guidance for method of protecting a plant against insect or nematode infestation by transformation with any nucleic acid encoding a cysteine protease inhibitor comprising a type I thyroglobulin domain. The instant specification also fails to provide guidance the hybridization conditions or probes or the PCR conditions or primers that can be used to isolate homologues of equistatin, or even which organisms have these homologues.

Making "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252) showed that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). Thus, making nucleic acids that encode functional derivatives of SEQ ID NO:2. would not be predictable.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate a multitude of nucleic acids that encode functional derivatives of SEQ ID NO:2. Making nucleic acids that encodes all possible single amino acids substitutions of a 199 amino acid long protein like SEQ ID NO:2 would require making analyzing 19^{199} nucleic acids.

Additionally, the instant specification does not teach the structural features that distinguish proteins with type I repeated thyroglobulin domains that control insects or are cysteine protease from those that proteins with type I repeated thyroglobulin domains but do not control insects and do not inhibit cysteine proteases.

Therefore, the claims are not enabled for a method of protecting a plant against insect or nematode infestation by transformation with any multitude of nucleic acids encoding a cysteine protease inhibitor comprising a type I thyroglobulin domain or a "functional derivative" of SEQ ID NO:2, plants and cells transformed with such nucleic acids, and expression vectors for that transformation.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 8-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections.

Claims 8-12 are indefinite because they lack agreement between the preamble of the methods and the positive method steps. Methods must be circular; the final step must generate

the item the method is intended to produce. For example, the method of protecting a plant in claim 8 ends in providing an insect or nematode controlling amount, when it should end in the production of protected plants.

It is not clear in claim 8 where the step of inserting occurs in relation to the presenting step of claim 1.

It is not clear in claim 9 where steps (a)-(c) occur in relation to the inserting step of claim 8. Also, it appears from the claim that a sequence coding for a protein with a type I thyroglobulin domain is put into the cells twice, once when it is inserted into the plant (claim 8) and once when it is introduced in to the cells (claim 9, part (b)).

In claim 9, part (a) it is unclear if "the plant" refers to the plant before insertion of the sequence or after.

Claim 9 lacks an antecedent basis for the limitations "the ... tissue" in part (b) and "the cell or tissue culture" in part (c).

Claim 10 recites the limitation "the whole plant" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim, as claim 9 regenerates whole plants.

Claim 10 lacks an antecedent basis for the limitation "the reproduction" in line 7.

It is not clear in claim 11 is the plant of step (a) is intended to be fertile and either insect or nematode resistant, or it the plant is tended to be fertile or insect or nematode-resistant.

Claim 11 lacks an antecedent basis for the limitations "the insect or nematode susceptible plants" and "the susceptible variety" in part (b).

The section criteria in claim 11, part (a) are unclear.

In claim 11, it is unclear to what the variety is susceptible.

In claim 12 it is unclear to what the method is directed. It appears to be a method a method of protecting a plant against insect or nematode infestation by transformation with a nucleic acid encoding a cysteine protease inhibitor comprising a type I thyroglobulin domain for imparting insect or nematode resistance to a population of plants. This makes no sense.

Claim 12 is indefinite in its recitation of "the other characteristics" in part (b). It is not clear what characteristics of the susceptible variety, other than insect or nematode resistance, are being selected for. Also it is not clear if Applicant intended to imply that the susceptible variety was resistant to insects or nematodes.

Claim 12 lacks an antecedent basis for the limitations "the insect or nematode resistant progeny" in part (a) and "the progeny of the backcross" in part (b).

A word appears to be missing between "progeny" and "resistant" in lines 1-2 of claim 13.

Claim 13 is indefinite in its recitation of "an insect of nematode controlling amount", which makes no sense. Should "of" be --or--?

In claim 14 "containing" and "composed of" should be replaced with --comprising--.

Claim 14 lacks an antecedent basis for the limitations "the genetic construction product" in lines 7-8, "the genetic construction" in line 8, "the protein containing" in line 10, and "the cells of the plant" in line 9. Correction will also be required in dependent claims.

In is not clear in claims 14-17 in what biological manner the expression vehicle is functional.

It is not clear in claim 15 in what manner the derivative is functional.

Claim 15 lacks an antecedent basis for the limitation "the DNA isolate" in line 15.

Claim 16 lacks an antecedent basis for the limitations "The biological functional expression vehicle" and "the expression vehicle".

Claim 18 lacks an antecedent basis for the limitations "The transgenic host cell" in line 1, "the DNA sequence" in lines 1-2, "the DNA sequence coding region" in line 4, and "the plant" in line10.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 15 and 17 rejected under 35 U.S.C. 102(b) as being anticipated by Walsh et al (WO 9221753).

Walsh et al teach a biologically functional plant expression vector encoding a cysteine protease (pg 73). This protease would be "functional derivative" of SEQ ID NO:2. Walsh et al also teach maize plants, and thus maize plant cells, transformed with this vector (pg 73-82).

18. Claims 8-14, 16 and 18 are free of the prior art, given the failure of the prior art to teach or suggest isolated nucleic acids encoding a cysteine protease inhibitor comprising a type I thyroglobulin domain.

Conclusion

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kimberly Davis, at (703) 305-3015.

Anne R. Kubelik, Ph.D.
April 8, 2002

AMY J. NELSON, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600